Clinical analgesic trials of NK_1 antagonists

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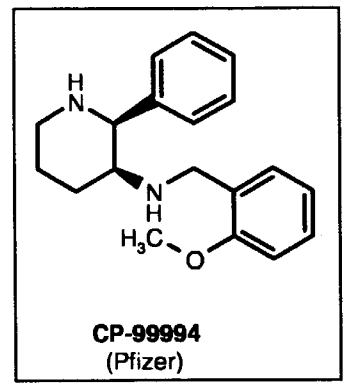
The wide distribution of substance P (SP) in the nervous system, including 45% of the cell bodies of small afferent neurons that respond to noxious stimuli, and demonstrations that direct application of SP onto these neurons produces excitation [1] and hyperalgesia [2-4] led to the hypothesis that SP is a mediator of pain transmission from primary sensory fibers. SP most avidly binds to the neurokinin-1 (NK_1) receptor, found on many spinal dorsal horn neurons that respond to noxious stimuli [2,5]. In addition to central postsynaptic effects, SP is released from peripheral nerve endings and may contribute to inflammation and sensitization of peripheral nociceptors by effects such as vasodilatation, increased vascular permeability, and release of inflammatory mediators from leukocytes and mast cells [6-8]. SP has also been implicated in the pain associated with migraine headaches by release, along with other inflammatory peptides, from inflamed dura to stimulate NK_1 receptors on the dural vasculature. This spectrum of distribution and activity of SP led to the development and clinical evaluation of NK_1 receptor antagonists for acute pain, migraine and inflammation.

CP-99994 in the oral surgery model

CP-99994 (Pfizer Inc; Figure 1), a non-peptide, selective antagonist of the NK_1 receptor, was one of the first drugs in this class to become available for human studies. It readily crosses the blood-brain barrier in animals [9], binds selectively and with high affinity to NK_1 receptors in a human cell line (K_d = 0.4 to 0.6 nM) [9] and produces analgesic effects in animal models [9,10]. In order to assess the effects of NK_1 antagonism on acute inflammatory pain, two double-blind, randomized, placebo-controlled trials compared the analgesic activity of pre- and post-operative intravenous infusion of CP-99994 to that of pre-operative ibuprofen and to placebo.

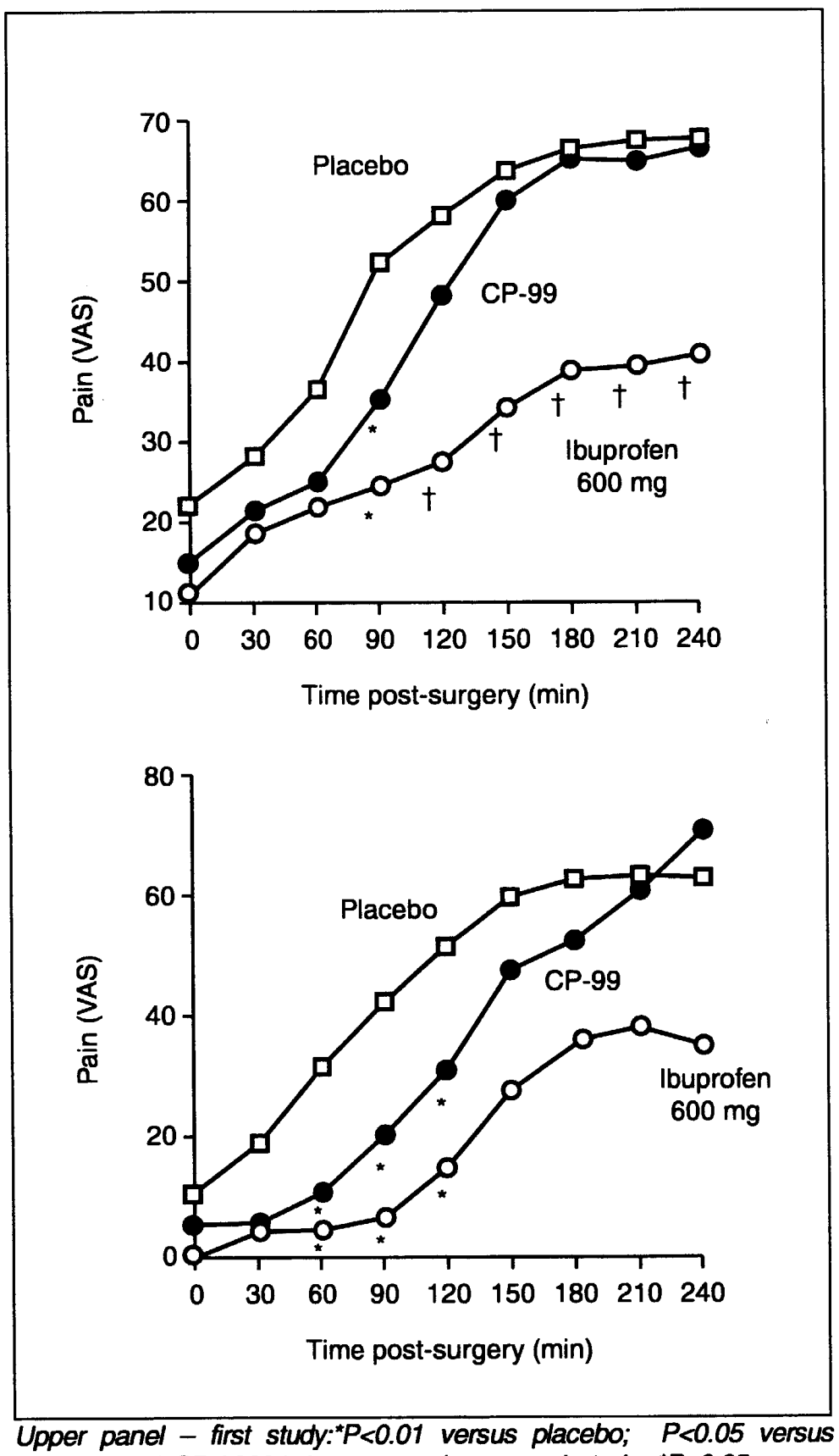
In the first study [11•] (N = 60), pre-operative administration of ibuprofen resulted in significantly less pain than placebo from 90 to 240 min post-surgery and in comparison to CP-99994, from 120 to 240 min. Pain intensity was significantly lower in subjects receiving CP-99994 compared to placebo only at 90 min following surgery. In the second study [11•] (N = 18), the drug infusion was changed to optimize circulating drug levels; both CP-99994 and ibuprofen suppressed pain, as measured by a visual analog scale in comparison to placebo at 60 to 120 min post-surgery, but did not differ significantly from each other.

Figure 1.



CP-99994
(Pfizer)

Figure 2. Analgesic efficacy of pre- and post-operative CP-99994



*Upper panel – first study:*P<0.01 versus placebo; P<0.05 versus placebo and CP-99994. Lower panel – second study: *P<0.05 versus placebo.*

(Reprinted with permission of Mosby Inc and R Dionne *et al.* **The substance P receptor antagonist CP-99994 reduces acute postoperative pain.** *Clin Pharmacol Ther* (1998) **64**:562-568)

The results of these two clinical studies provide the first data supporting the hypothesis that SP is involved in the generation of pain in humans and demonstrate that the non-peptide antagonist CP-99994 relieves pain at doses that do not appear to cause significant side-effects. In both trials, significant pain relief was only seen whilst CP-99994 was being infused at a rate of ≥ 100 μg/kg/h, indicating that the analgesic effect of CP-99994 is rapidly reversible after plasma levels decline (Figure 2).

Evaluation of lanepitant for chronic pain

Lanepitant (Eli Lilly & Co; Figure 3) is a high-affinity, non-peptide, competitive NK_1 receptor antagonist which is effective in the guinea pig model of dural inflammation. Its effectiveness for acute migraine was evaluated in humans following headache onset administered as single oral doses of 30, 80, or 240 mg compared to placebo in a crossover study (N = 40) [12]. None of the doses showed different response rates from placebo, for either the whole crossover period or for the first blinded dose. No differences were observed among the four treatments in the need for rescue medication (71 to 82% of lanepitant-treated subjects versus 75% on placebo) or for the patients' global impression of improvement. The authors note that absorption of lanepitant is significantly impaired during a migraine attack, suggesting the possibility that plasma concentrations may have been inadequate. Alternatively, the dural inflammation model may not accurately predict the efficacy of migraine treatments such that lanepitant may be active in this model but ineffective in the therapy of acute migraine.

A second study [13•] compared prophylactic administration of 200 mg lanepitant to placebo for migraine frequency and severity following a one-month placebo period. Whilst the drug was well-tolerated, no efficacy variables differed significantly between treatments. Since the absorption was not impaired by gastric stasis associated with the migraine attack, the lack of effect was probably due to ineffective NK_1 blockade rather than insufficient plasma concentration.

Based on activity in the formalin paw analgesic model, lanepitant was also evaluated for painful diabetic neuropathy. Subjects (N = 93) were randomly allocated to doses of 50 mg daily, 100 mg daily, or 200 mg twice daily, in comparison to placebo over 8 weeks [14]. Analgesic efficacy did not increase with lanepitant dosage and no dose was significantly different from placebo; higher plasma concentrations were no more effective than lower concentrations. Whilst lanepitant was safely administered, diarrhea was more frequent in the drug-treated group. Lanepitant (10, 30, 100, or 300 mg) was also ineffective for osteoarthritis (OA) [15] in comparison to placebo and naproxen (Elan Corp plc) in patients (N = 214) with moderate to severe lower limb OA in a 3-week trial. Naproxen treatment resulted in significantly less pain than placebo, indicative of a sensitive bioassay, but lanepitant did not differ from placebo. Whilst ineffective in relieving OA pain, lanepitant was again associated with diarrhea.

L-754030 in the oral surgery model

Another NK_1 receptor antagonist, L-754030 (MK-869; Merck & Co Inc; Figure 4), was also evaluated in the oral surgery model with the results reported in abstract form [16]. A sensitive bioassay was demonstrated for 800 mg ibuprofen administered prior to surgery over the course of 8 h post-surgery. Administration of L-754030 (300 mg) 2 h prior to surgery could not be differentiated from placebo at any time point, leading to the conclusion that the drug is not effective for post-oral surgery pain as a single post-operative dose.

Figure 3.

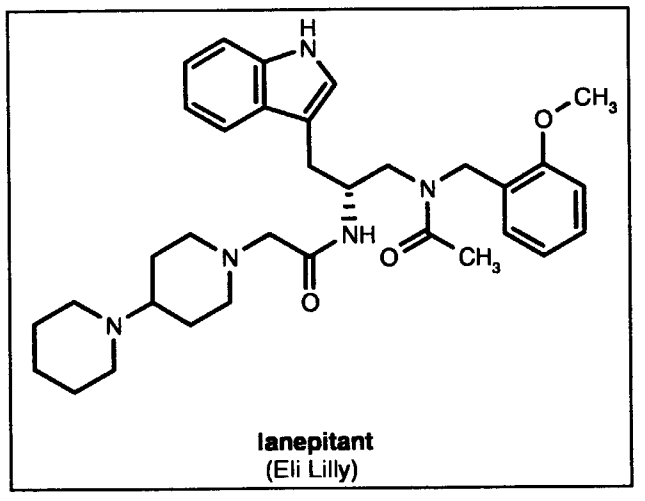
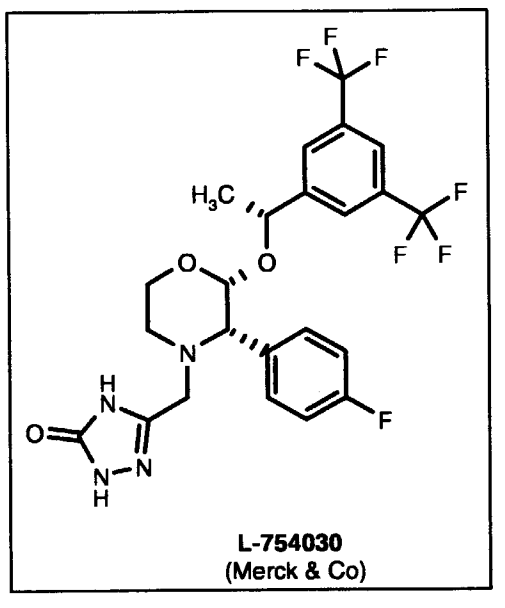


Figure 4.



NK_1 receptor antagonists for acute and chronic pain

Of the three selective NK_1 receptor antagonists evaluated in published clinical trials, only CP-99994 demonstrated transient analgesic activity in a clinical model of acute pain. Lanepitant administration in doses which were well-tolerated up to a dose which produced diarrhea was ineffective for acute migraine and migraine prophylaxis, diabetic neuropathy and OA. L-754030 was also ineffective as a single dose in the oral surgery model. These weak, equivocal clinical results for NK_1 receptor antagonists across a variety of conditions contrast with related animal models [17] and are not predictive of clinical utility.

A possible reason for observing relatively modest effects of specific NK_1 antagonists may be that many neurotransmitters besides SP contribute to the generation of pain. This explanation is supported by animal studies indicating that intrathecal administration of NK_1 antagonists rarely yields more than 50 to 80% inhibition of hyperalgesia in various models of paw inflammation [18-20], and analgesia diminishes or disappears if larger doses of the pro-inflammatory substance are used [18].

A further explanation for the modest analgesic effect of NK_1 antagonists given immediately before and after surgery is that SP may not become a major contributor to pain until many hours or days after an injury. For example, the number of NK_1 receptors in the spinal dorsal horn increases one day after injection of complete Freund's adjuvant into the paw, and three days after sciatic nerve section [21]. Local inflammation also produces an increase in SP content of spinal nerves and dorsal horn [22,23], in part by causing myelinated primary sensory neurons which normally mediate light touch to begin producing SP [24••]. This phenotypic switch, mediated partly by nerve growth factor, reaches a maximum at 48 h [25], the time at which clinical manifestations of surgically-induced inflammation also reach a peak [26]. Greater analgesia than that demonstrated in acute pain studies may be observed if NK_1 antagonists are administered during later phases of post-operative inflammation in chronic inflammatory conditions such as rheumatoid arthritis and degenerative spinal disc disease, or in fibromyalgia, a syndrome in which elevated levels of cerebrospinal SP are present [27,28].

The nociceptive effects of the SP-NK_1 receptor interaction appear to enhance the action of other nociceptive mechanisms, such as the glutamate-NMDA receptor system [29,30], raising the possibility that combinations of antagonists will be useful. Because the analgesic effects of currently-available NMDA receptor antagonists are limited by dissociative and sedative side-effects [31-33], NK_1 receptor blockade might be a less toxic indirect method of reducing NMDA receptor activation. Combinations of NK_1 antagonists with NK_2 or NMDA receptor antagonists or other analgesic drugs such as non-steroidal anti-inflammatory drugs, opioids, or AMPA/kainate receptor antagonists might therefore allow greater levels of analgesia at tolerable doses. Whilst the early clinical investigations of selective NK_1 antagonists are equivocal, the opportunities offered by these antagonists and other new analgesic candidates should stimulate the systematic investigation of analgesic combinations in human pain models for possible efficacy in particular clinical pain syndromes.

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